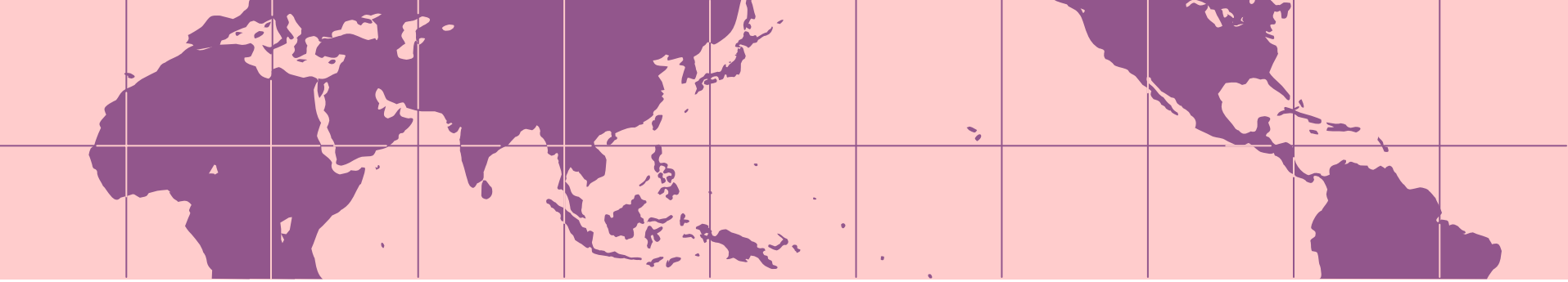


HIV/AIDS Clinical Research Networks

2006 - 2013

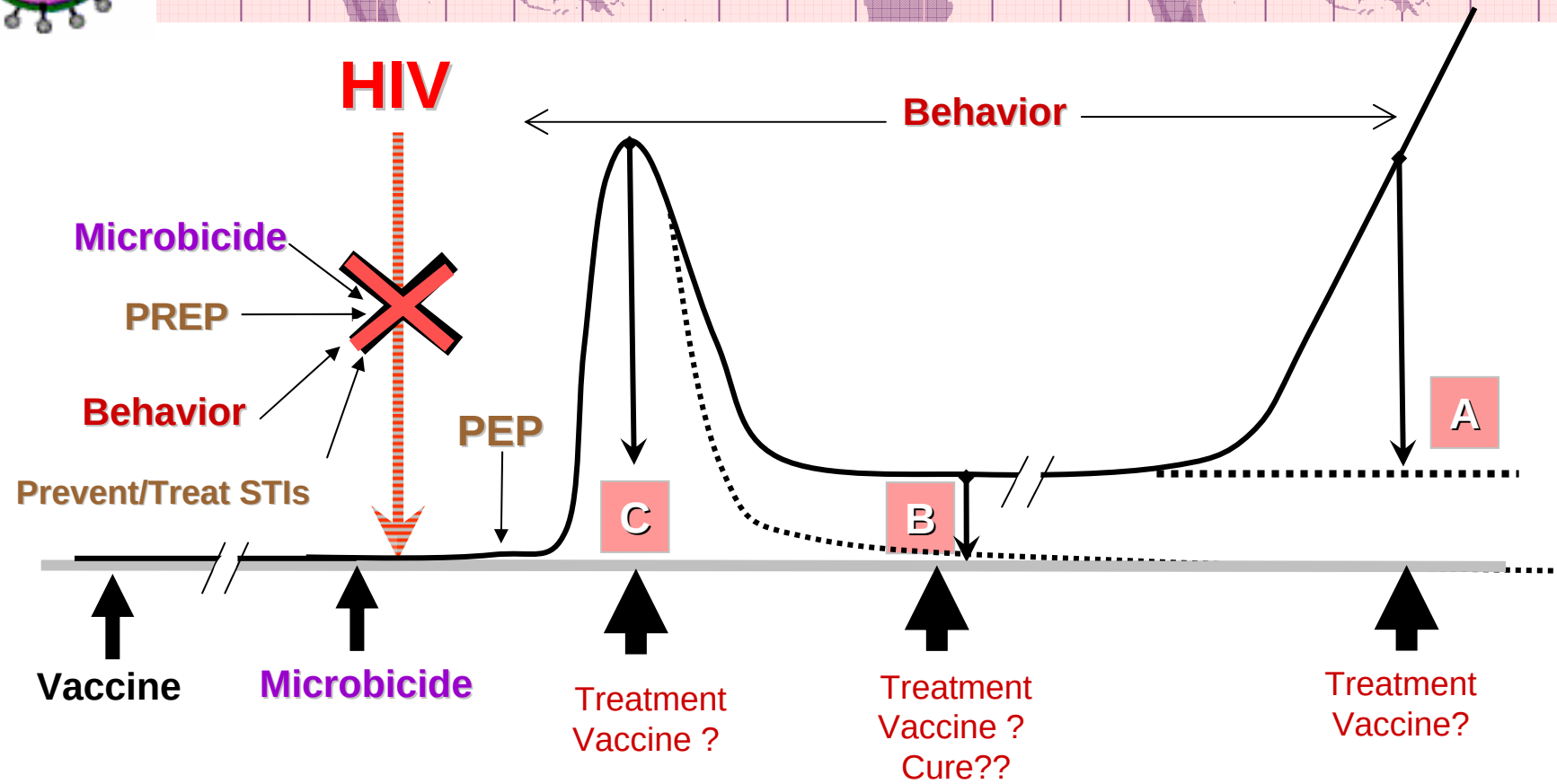
DAIDS Scientific Priorities

NIAID Pre-application Meeting
December 13, 2004

Agenda-overview

- Scientific framework
- Areas of scientific emphasis
- Cross-cutting principles, coordination and collaboration

DAIDS Mission: Help Stop the HIV/AIDS Epidemic

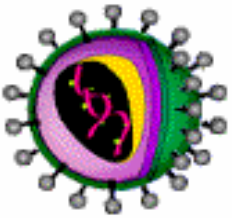


Populations: Adults, Infants, Children, Adolescents

A. Stop Progression, Development of Resistance

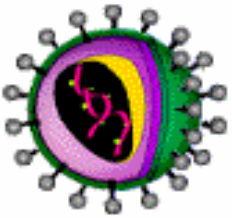
B. Lower Set Point or Eliminate HIV

C. Lower Initial Peak of Viremia



Over-arching Goals of the RFA

- Establish a consortium of linked clinical trials networks
- Implement a comprehensive clinical research agenda
- Coordinate activities across networks to ensure high caliber science
- Increase efficiency through resource sharing;
- Flexibly allocate and distribute resources in response to evolving priority research opportunities
- Leverage resources within and outside the networks



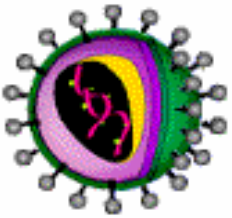
Areas of Research Emphasis

- Vaccine Research and Development
- Translational Research / Drug Development
- Optimization of Clinical Management, Including Co-Morbidities
- Microbicides
- Prevention of Mother-to-Child Transmission (MTCT) of HIV
- Prevention of HIV Infection

Color Scheme

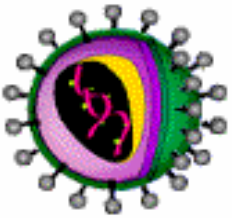
- **Black = Highest priority for NIAID**
- **Grey = Will require partnering and/or additional resources to fully accomplish**
- **Blue = NIH research partners**

Vaccine Clinical Research



Vaccine Research and Development: Objectives

- Identify a vaccine that is safe and effective (at least partially)
- Benefit the individual, e.g. infection or disease progression
  - Reduce/prevent secondary transmission
- Decipher correlate(s) of immune protection
- Improve in vaccine design, e.g. clades, routes

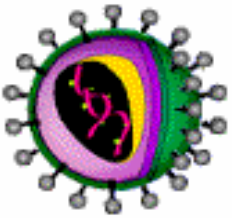


Vaccine Clinical Research

- **Evaluate/compare selected candidates in phase 1 and 2 trials (VRC, Grantees, Companies, Non-profits, EU, Others)**
  - **Safety**
  - **Immunogenicity: qualitative and quantitative**
    - **Systemic and mucosal**
    - **Humoral and cellular**
- **Link with vaccine designers**
  - **Anti-vector immunity**
- **Down select and advance most promising candidates**

Vaccine Clinical Research

- **Evaluate candidates into phase 2b/3**
  - **Test candidates for efficacy; include women, and minorities**
  - **Identify immunologic correlate(s) of protection**
- **Link with cohort/epi studies to prepare populations; consider community trials as warranted; adolescents (NICHD/ATN)**
- **Implement strategy to ensure rapid licensure in special populations and all at-risk groups, including adolescents (NICHD/ATN)**



Vaccine Clinical Research

- **Develop and conduct lab assays to evaluate immune responses and compare candidate vaccines**
  - **Validate assays to be used in pivotal trials**
  - **Develop methods to optimize signal (collection, processing, freezing, shipping) (peptide pools to make relevant comparisons)**
  - **Implement QA/QC programs**
  - **Develop new assays to measure full breadth of induced immune responses**

Vaccine Clinical Research

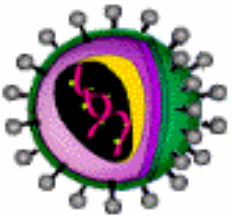
- **Develop novel trial designs**
  - **Develop strategies to standardize, optimize trials**
  - **Optimize designs to accelerate licensure**
- **Contribute to discussions on trial design to facilitate US and international licensure**

Vaccine Clinical Research

- Link with animal model studies
- Decipher relevance of genetic subtypes
- Evaluate host factors that may impact outcomes (e.g. gender, HLA, etc)

Vaccine Clinical Research

- Pursue innovative approaches e.g. mucosal immunity, combinations, enhanced innate immunity, novel vaccines such as regulatory proteins **(NCI)**
- Oral and nasopharyngeal routes/adjuvants (**NIDCR**)
- Explore factors that affect understanding about product efficacy, acceptance, use; impact on risk reduction (**NIMH**)
- Explore factors that affect understanding about product efficacy, vaccine use (**NIMH**)

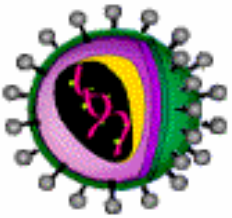


Vaccine Clinical Research

- **Transparency, cooperation, collaboration**
- **Work with others on HIV vaccine R&D, e.g. PAVE, Enterprise**
  - **Lab assays, reagents for cross-system comparisons**
  - **Clinical site development, training, etc.**
- **Link with others**
  - **Vaccines for prevention of MTCT**
  - **Therapeutic vaccines**
  - **Cancer vaccines (NCI)**
  - **Care and treatment programs in resource poor settings**

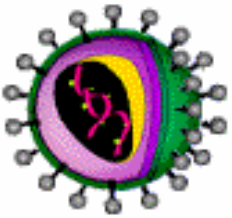
Therapeutics Clinical Research

- Translational Research / Drug Development
- Optimization of Clinical Management



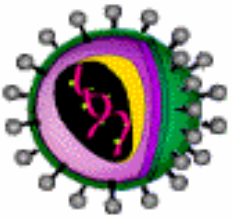
Therapeutics Clinical Research: Objectives

- **To prevent HIV disease progression and deaths**
  - **Through the development of innovative strategies for antiretroviral treatment (ART) that provide *optimum* initial and subsequent ART regimens**
  - **Through effective use of new agents or novel classes of antiretroviral drugs, as they are developed**



Therapeutics Clinical Research: Objectives

- To identify, prevent and treat the complications of both HIV disease and antiretroviral therapies
- To prevent transmission of HIV infection and emergence of drug resistant virus in the community through therapeutic intervention
- Ultimately - CURE



Therapeutics Clinical Research: Overarching Principles

- Identify underserved or disenfranchised populations (e.g. women, minorities, adolescents, young children)
- Specify barriers to participation in clinical research for these and other special populations
- Develop strategies to address the problems identified above

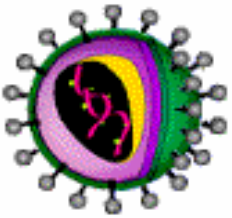
Therapeutics Clinical Research: Overarching Principles

- **Incorporate studies of acutely infected individuals in all aspects of research – particular focus on role of early interventions in modifying viral set point, long term outcome and transmission rates**

- **Pharmacogenomics – Investigate the role of individual and population genetic differences in responses to therapy, incidence of complications, and course of disease**

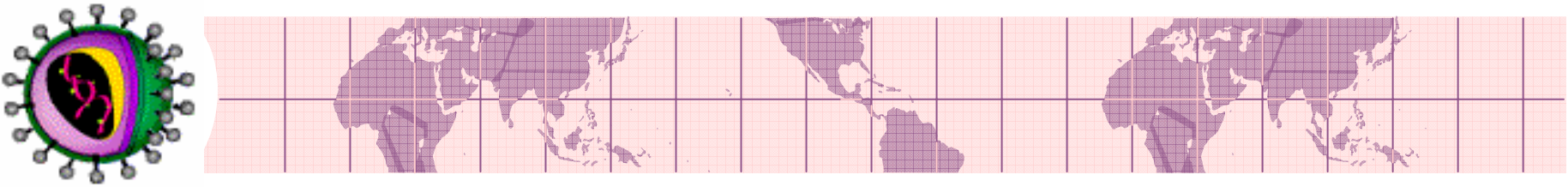
Translational Research: Drug Development

- Evaluate anti-HIV compounds aimed at novel mechanisms of action/new targets including small molecule entry inhibitors, uncoating inhibitors, integrase and maturation inhibitors
- Evaluate new molecules with unique and improved features (resistance, pharmacology, toxicity profiles)



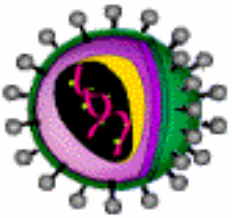
Translational Research / Drug Development

- Evaluate therapies for patients with co-infections, especially Hepatitis C, Tuberculosis, Malaria and Papillomavirus infections
- Focus on studies that address the highest public health needs and which expand and complement studies being conducted by pharmaceutical industry



Translational Research / Drug Development

- Integrate immune-based therapies in treatment regimens, emphasizing mechanisms of antiviral effect and immune reconstitution
- Conduct pharmacokinetic studies in children and adolescents to enable licensure and optimize use
- Test new hypotheses generated by pathogenesis studies

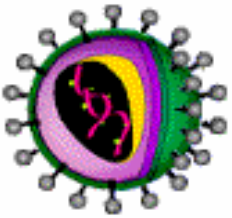


Translational Research / Drug Development

- With **NICHD** address research agenda relevant to pregnant women, children and adolescents – especially pharmacokinetics and safety data relevant to licensure and optimum use in these populations
- With **NCI** implement studies in areas of mutual scientific interest - especially HPV and Hepatitis

Translational Research / Drug Development

- Study aspects of HIV pathogenesis including viral evolution, host response, elimination of viral reservoirs and co-factors which influence response to therapy in treated subjects



Optimization of Clinical Management

- Study effectiveness of new regimens, focusing on agents with novel mechanisms of action or new treatment combination strategies
- Optimize therapies on the basis of safety, adherence, resistance, durability of response and prevention of transmission
- Evaluate therapies and therapeutic strategies for co-infections

Optimization of Clinical Management

- **Evaluate therapies and therapeutic strategies for co-infections**
  - **Prophylaxis**
  - **Acute treatment**
  - **Interaction with antiretroviral agents.**

Optimization of Clinical Management :

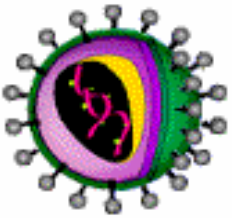
With NCI, NIDDK, NHBLI, NIMH, NINDS

- Integrate studies of malignancies, particularly KS and those associated with viral hepatitis, papillomavirus, and EBV into research agenda
- Facilitate treatment and evaluation of metabolic abnormalities and other complications of ARV therapy and/or progressive HIV infection – with other ICs with special expertise

MTCT Research

Mother to Child Transmission (MTCT) Research: Objectives (NICHD)

- Identify safe, practical, and more effective approaches to further reduce MTCT, especially in resource-poor settings and breastfeeding populations
- Define treatment options and adherence approches for both mother and child (separately and as a unit)
- Provide technical knowledge to ensure prolonged success of MTCT programs

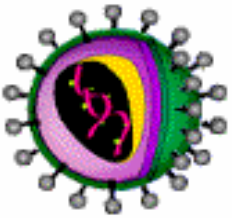


Prevention of Mother-Child Transmission (and Impact on Future Treatment) (NICHD)

- **Strategies to optimize and simplify regimens to prevent MTCT** (when mothers not on drug for their own disease)
  - **Maternal and infant treatment, especially during breastfeeding period**
  - **Minimize drug resistance and drug toxicity (esp high CD4 moms)**
  - **Evaluate impact of drug resistance on treatment option of mothers, children, and communities; options for future pregnancies**

Prevention of Mother-Child Transmission (and Impact on Future Treatment) (NICHD)

- **Strategies to optimize drug regimens pre-, peri- and post-partum** (when mothers on drug for their own disease)
  - Further decrease transmission rates
  - Prevent drug resistance
  - Minimize toxicities
  - Simplify delivery
  - Evaluate the development and impact of resistance on MTCT and future treatment options for mother and child



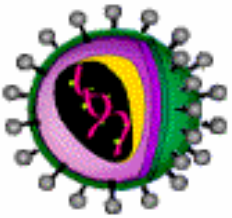
Prevention of Mother-Child Transmission (and Impact on Future Treatment) (NICHD)

- Evaluate safety and PK of new drugs, drug combinations
  - HIV negative, non-pregnant women
  - HIV positive, non-pregnant women
  - HIV positive, pregnant women
  - HIV positive, very young children
- Improve strategies for interruption of transmission via breast milk

Prevention of Mother-Child Transmission (and Impact on Future Treatment) (NICHD)

- Safety and efficacy of vaccines to prevent BF transmission
- Safety and efficacy of passive immunization of newborns

Microbicide Research

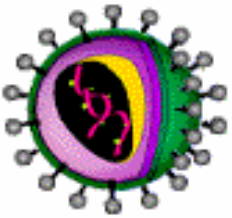


Microbicide Clinical Research and Development: Objectives

- Identify a microbicide that is very safe and effective (at least partially)
- Determine correlates of short and long term safety
- Optimize acceptability and adherence

Microbicide Clinical Research (DMID, NICHD)

- Conduct all phases of clinical research
  - Focus on products with appropriate safety profile (daily use), multiple mechanisms of attack; combinations
    - X4/R5 HIV; resistance; other STIs; high vs low frequency users; adolescents; conception/pregnancy
  - Phase 1-2
  - Evaluate best 2-3 in phase 2b/3 trials
- Transparency, cooperation and collaboration

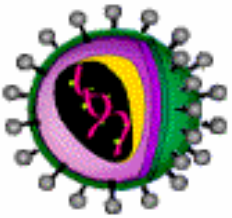


Microbicide Clinical Research (NICHD, CDC, USAID)

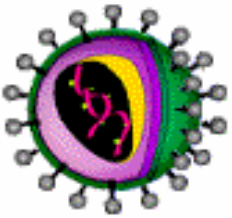
- Explore correlates of safety (and efficacy)
- Evaluate user and partner acceptability and adherence; short and long term; behavioral and cultural factors (NIMH)
- Evaluate consequences of microbicide use
  - Impact on other risk reduction measures (e.g. sexual risk negotiation in the context of microbicide use)

Microbicide Clinical Research

- Evaluate novel delivery approaches; single formulation; intercourse dissociated
- Conduct research on rectal products (safety)
- Evaluate impact on other STDs, immune responses, vaginal defenses
- Evaluate novel strategies to protect newborns from orally acquired HIV (**NIDCR**)

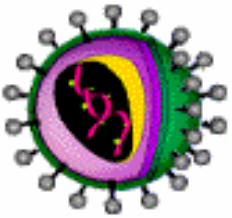


Prevention Research



Prevention Clinical Research: Objectives

- Identify more practical, safe and effective approaches to halt the spread of HIV
  - Especially in populations where HIV is spreading most rapidly
- Generalizable and feasible to scale up and sustain



Prevention Research

- **ART to prevent transmission**
  - **ART or ART combination intervention in acute/early infection**
    - **Identify approaches to identify, recruit and retain individuals acutely infected with HIV, particularly in resource limited settings**
    - **Evaluate impact in primary infection on transmission and disease progression; resistance; immune responses, etc**
  - **ART in established infection**
  - **PEP and PREP**

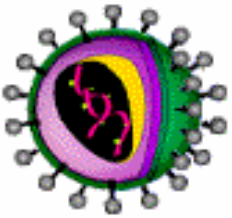
Prevention Research

- **Treatment or prevention of STDs that are co-factors in HIV transmission and/or acquisition (DMID, NIMH)**
  - **Pharmacologic, vaccines, behavioral, surgical**
- **Interventions to reduce HIV acquisition or transmission in drug users; linked biomedical and behavioral interventions (NIDA)**
- **Impact of alcohol consumption on transmission (NIAAA)**

Prevention Research

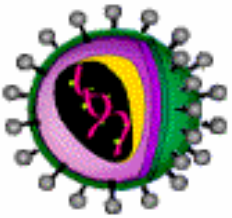
- Efficacious, cost-effective, sustainable, behavior interventions to reduce risk behaviors AND HIV acquisition or transmission (**NIMH, NINR**)
  - Individual and/or community, including adolescents (**NICHD/ATN**)
  - VCT uptake; abstinence messages; ART availability; sex education
  - "Dosage"; "delivery"; "durability"

- **Coordinate with care and treatment programs in resource limited settings**



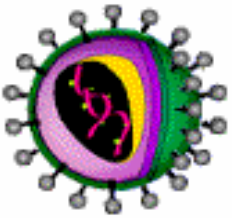
Cross-Cutting Principles

- Identify underserved or disenfranchised populations (e.g. women, minorities, adolescents, young children)
- Specify barriers to participation in clinical research for these and other special populations
- Identify highest risk populations to size and cost of vaccine and prevention efficacy trials (epi, incidence)
- Behavioral interventions in all studies (**NIMH, NIDA**)



Cross-Cutting Principles

- Feed information on seroconverters in vaccine/prevention studies into acute infection data base or studies
- Refer HIV+ during screening to treatment programs or research studies
- Develop common laboratory and data management elements
- Establish a system for address important questions that cannot be studied by a single group
- Genomics – Investigate the role of individual and population genetic differences in resistance/susceptibility to infection, responses to therapy, incidence of complications, and course of disease



Coordination and Integration between Networks-starting points

- Share laboratory resources and protocols for data comparability and efficiency
- Work towards common data entry interfaces and data elements
- Coordinate specimen management
- Share and/or standardize training for common needs
- Shared responsibility for sites
- Coordinate clinical research product acquisition, distribution and provision
- Increase inter-network communication
- Become more efficient with all resources